Determining the optimal tranexamic acid dose for cardiac surgery with cardiopulmonary bypass：A randomized controlled trial

Running title: tranexamic acid application

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Conflict of Interest

The authors declare no conflicts of interest.

ABSTRACT

Background: Tranexamic acid (TXA) has been widely used to reduce the risk of bleeding in patients undergoing cardiac surgery. However, the clinical TXA dose that best reduces postoperative bleeding has not been determined. We evaluated the efficacy of two different doses of TXA using Thromboelastography (TEG) in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Methods: One hundred and eleven patients who underwent primary cardiac valve replacement with CPB were enrolled in this study. Patients were randomly divided into three groups: T_1, T_2, and the control group. Patients in the TXA group would receive different TXA doses: 15 mg/kg loading dose followed by an infusion of 5 mg/kg/h until the completion of surgery (T_1 group) or 6 mg/kg loading dose followed by an infusion of 3 mg/kg/h until the completion of surgery (T_2 group). Pre-operative patient characteristics, intraoperative data, transfusions between and after surgery, chest tube output after surgery within two days, and outcome data were recorded.

Results: Transfusion of blood products, blood loss, and chest tube output were significantly reduced in the T_1 group compared with the control group ($P< 0.05$). Compared to the control group, the T_2 group had similar results. Surgical time and length of intensive care unit (ICU) stay were significantly lower in the T_1 and T_2 groups compared to the control group ($P< 0.05$). No postoperative seizures

occurred in all three patient groups.

Conclusions: The use of Tranexamic acid was associated with a lower risk of bleeding compared to the control group. Both doses of tranexamic acid were effective to reduce blood loss as well as transfusions compared to the control group.

Keywords: Tranexamic acid, cardiac surgery, CPB, transfusion, Thromboelastography

BACKGROUND

Excessive bleeding and blood transfusions are common problems in patients undergoing cardiac surgery.(1) With regards to patient blood management, administration of blood transfusions are common interventions during surgery.(2) Excessive bleeding increases the risk of complications and may require the need for additional surgeries. In some clinical situations, fresh frozen plasma (FFP) may be transfused when a large amount of blood is required. However, the clinical effectiveness of fresh frozen plasma treatment lacks a scientific basis.(3) Based on a published meta-analysis, fresh frozen plasma should not be used prophylactically to supplement blood volume. (4)

In patients undergoing cardiac surgery with CPB, many risk factors may lead to excessive bleeding. Studies have shown that some important risk factors for increased bleeding during and after

cardiac surgery include advanced age, low body surface area, emergency surgery, low-temperature environment during CPB, and the duration of cardiopulmonary bypass.(5)Hence, antifibrinolytic agents have been commonly used to reduce bleeding as well as decrease the exposure to blood products during cardiac surgery. Although aprotinin has been effective in reducing bleeding compared to other active agents, it has been associated with an increased risk of mortality and hence has been replaced with lysine analogs. (6) Furthermore, a high-dose protocol of TXA（≥100mg / kg）has been associated with an increased rate of seizures(7). However, TXA has not been associated with a higher risk of death or thrombotic complications in patients undergoing coronary artery bypass graft (CABG).(8)Greiff et al(9) demonstrated that tranexamic acid could reduce red blood cell infusion in elderly patients aged 70 years or older undergoing combined aortic valve replacement and coronary artery bypass graft surgery. However, the appropriate dose of TXA that could effectively control hemostasis remains to be determined. Previous reports have supported that using a low-dose TXA protocol was equivalent to a high-dose TXA protocol among patients undergoing primary CABG with CPB.(10)

Cardiac surgery with CPB has been associated with reduced blood generation and complex alterations in hemostasis. Thromboelastography was initiated in 1948 by Hartert and provides an alternative method for perioperative hemostasis assessment.(11) To achieve sufficient hemostasis it is

necessary to maintain an appropriate level of coagulation factors in the body. TEG helps to evaluate almost all the components of the hemostatic system and it has been helpful to identify target patients to receive antifibrinolytic therapy.(12)

This study was performed to assess the blood-conserving effect of two doses of TXA and used thromboelastography to evaluate the coagulation function of patients. This was performed to improve perioperative blood transfusion in patients undergoing surgery.

METHODS

Study Design

This study was a prospective, randomized controlled trial that compared two doses of TXA in adult patients who underwent cardiac surgery with CPB. The study conformed to the principles of the Declaration of Helsinki. The study was approved by the clinical medical research Ethical Committee of The First Affiliated Hospital of Anhui Medical University(PJ-06-12(1)) and was registered at the Chinese Clinical Trial Registry (Registration number: ChiCTR-IOR-17012425) on August 21, 2017. All patients signed informed consent. Based on the random number table method, patients were randomly assigned into three groups: T_1, T_2, and the control group.

Participants

Eligible patients who underwent elective surgery for cardiac valve replacement with CPB from The First Affiliated Hospital of Anhui Medical University were enrolled in this study. The randomization sequence of the three groups was based on the random number table using a distribution ratio of 1:1:1. The participants, investigators were unaware of the trial but the medical staff knew the test group. The study started on November 2017 and ended on March 2019. Patients aged between 20-70 years old were enrolled. Inclusion criteria were patients who satisfied the American Society of Anesthesiologists (ASA) grades II or III and the classification of the New York Heart Association (NYHA) heart function grades II or III. All patients had no history of preoperative convulsion. Exclusion criteria were patients with previous cardiac surgery, left ventricular ejection fraction <40%, preoperative coagulopathy, and allergy to tranexamic acid. Patients with liver or kidney dysfunction and those treated with dual-antiplatelet therapy within 7 days before surgery were excluded. In addition, patients undergoing additional procedures such as coronary artery bypass was excluded.

Anesthesia and CPB Management

Anesthesia was induced using midazolam 0.02mg/kg. Propofol was administered by target controlled infusion (TCI). The initial propofol target-controlled plasma concentration was set to 1.0 μg/ml and was increased by 0.3 μg/ml every minute until loss of consciousness (loss of consciousness

was determined by the patient's loss of response to verbal instructions and eyelash reflex). After the loss of consciousness, the analgesic sufentanil 0.8~1.0μg/kg and the muscle relaxant rocuronium 0.6~0.9 mg/kg was administered.

After anesthesia induction, patients who underwent cardiac surgery via sternotomy received a 400U/kg heparin that was administered by intravenous injection after incision of the pericardium to achieve a target activated clotting time (ACT) >480s. CPB was then established. ACT was repeatedly checked to maintain ACT >480s by heparin appended when necessary during CPB. Protamine sulfate was administered to reverse the effect of heparin after CPB (1 mg/100 U of heparin). This was repeatedly administered based on ACT values compared to basal values. Attention was also paid to the risk of heparin residues. If the activated clotting time was significantly prolonged, a small dose of protamine (5-10 mg) was used to antagonize and restore the activated clotting time to within 10% of pre-heparin levels. The hemoglobin concentration at the end of cardiopulmonary bypass was then recorded. The amount of intraoperative blood loss was estimated based on the speed of intraoperative blood bleeding, the amount of blood-soaked in gauze, the drainage volume in the aspirator bottle, and hemoglobin levels. If hemoglobin levels were lower than 80 g/l and (or) if there was significant bleeding, blood transfusion was performed. A cell salvage was used to retrieve excessive blood when necessary. Salvaged blood was then reinfused back into the patient. Vasoactive drugs were used based

on the surgical procedure, the patient's heart rate, and blood pressure. Nitroglycerin was routinely used during cardiovascular anesthesia. This was because nitrate drugs could reduce myocardial oxygen demand by reducing cardiac preload and ventricular pressure. In addition, it can increase the blood flow ratio between the endocardium and epicardium. However, hypotension should be prevented by the use of Dobutamine, which is a positive inotropic drug that increases myocardial contractility by stimulating myocardial β1 receptors. It also reduces peripheral resistance and wall tension. After surgery, patients were transferred to the intensive care unit (ICU). All patients were routinely extubated in the ICU and postoperative care was carried out by a professional team of cardiac surgery.

Intervention

Patients in the T_1 group received a 15 mg/kg loading dose before skin incision followed by a continuous intravenous pump of 5mg/kg/h until the end of surgery. The T_2 group received a 6 mg/kg loading dose before skin incision followed by a continuous infusion of 3 mg/kg/h until the end of surgery. The control group was not administered tranexamic acid. TEG measurements were performed to evaluate the hemostatic system before and after surgery in all patients.

Thromboelastogram Test

ATEG 5000 thromboelastography analyzer (Haemoscope Inc, USA), a kaolin activator was used.

The six main parameters for TEG were recorded and included: R (coagulation reaction time with a normal value of 5 ~ 10 minrefers to the time required from the beginning of blood sample detection to fibrin formation). K (coagulation time, which refers to the time from the start of coagulation until the amplitude of the thromboelastogram tracing reaches 20 mm with a normal value of 1 to 3 minutes). α-Angle (the coagulation angle refers to the angle between the tangent and the horizontal line from the point of the blood clot formation to the maximum curve radian of the thromboelastogram. It represents the rate of blood clot formation. The normal value was 53 °~ 72 °). When K values were greater than 4 min and (or) α-Angle was lower than 48 °, it indicated low fibrinogen function. When K values were less than 1 min (and) or α-Angle was greater than 73 °, it indicated fibrinogen hyperfunction. MA (the maximum amplitude that reflects the absolute strength of the blood clot with a normal value of 50 ~ 70 mm). When MA values are lower than 45 mm, it indicates low platelet function, while MA greater than 72 mm indicates enhanced platelet function. LY30 (fibrin dissolution rate 30 minutes after MA determination with a normal value of 0 ~ 7.5%). When LY30 values are greater than 8%, it indicates that fibrinolytic function is hyperactive. When the R value of CK> R value of CK-H is more than 2 minutes, and greater than 10 minutes, it indicates the presence of heparin residues. When CI (coagulation index with a normal value of -3 to 3)is lower than -3, it indicates hypo coagulation, and when CI value is greater than 3, it indicates hypercoagulation.

Data Collection

Pre-operative information consisted of the patient characteristics, left ventricular ejection fraction, laboratory data (hemoglobin, hematocrit, platelet counts, INR, fibrinogen), and TEG parameters (r, MA, LY30). The duration of the surgical procedure and CPB, aortic cross-clamping time, and transfusions during the surgery were recorded. The hemoglobin levels after the termination of CPB were also recorded. Postoperative information included the chest tube output, blood product transfusions within 3 days, and length of ICU stay. Postoperative extubation time and chest drainage volume are recorded by professional nurses who were blinded to the test. Postoperative seizures and re-exploration for bleeding as well as post-operative laboratory data (hemoglobin, hematocrit, platelet counts, INR, fibrinogen) and TEG parameters (r, MA, LY30) were recorded. The primary outcomes of the trial were intraoperative and postoperative blood product transfusions and postoperative chest tube output. The secondary outcomes included length of ICU stay, re-operations, and incidence of epilepsy.

Statistical Analyses

Normally distributed measurement data were summarized as mean with standard deviation. Categorical variables were presented as frequencies (n%). For continuous variables, the comparison among the three groups was assessed using One-way analysis of variance. Categorical variables were

analyzed using a chi-square test. $P<0.05$ was considered statistically significant. All statistical analyses were performed using Graphpad Prism 8.0 statistical package.(Graphpad Software, LA Jolla, CA, USA.)

RESULTS

A total of 111 patients were included in this study and included 22 male and 18 female patients in the T_1 group. The T_2 group included 19 male and 17 female patients. There were 19 male and 16 female patients in the C group. Data from all 111 patients were analyzed. The randomisation flowchart as per CONSORT 2010 Guidelines is shown in Figure 1.

Patient Characteristics and Perioperative Data

There were no significant differences in patient baseline characteristics including age, gender, ejection fraction among the three groups (Table 1). There were no significant differences in preoperative laboratory tests among the three groups, which included hemoglobin (HB), hematocrit (Hct), platelet (PLT), activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen levels (FIB). This indicated that there were no significant differences in blood coagulation status among the three groups ($P>0.05$) (Table 2).

There were no significant differences in aortic occlusion time, CPB time, and protamine dosage in three groups of patients. Hemoglobin levels at the end of CPB in the T_1 group were higher compared to the C group (94.63±10.03 vs 81.36±9.36, $^aP<0.05$). This indicated that blood loss during CPB in the T_1 group was lower compared to the control group. In addition, hemoglobin levels at the end of CPB in the T_2 group were higher compared to group C (92.85±8.90 vs 81.36±9.36, $^aP<0.05$). Compared to the T_1 group, there were no statistically significant differences in hemoglobin levels at the end of CPB in the T_2 group (94.63±10.03 vs 92.85±8.90, $^bP = 0.76$). The intra-operative blood transfusion volume in the T_1 group was lower compared to the C group (518.2±232.8 vs 741±190.8, $^aP<0.05$). The intraoperative blood transfusion volume was also lower in the T_2 group compared to the C group (550±242.5 vs 741±190.8, $^aP<0.05$). Compared to the T_1 group, there was no significant difference in intraoperative blood transfusion volume in the T_2 group (518.2±232.8 vs 550±242.5, $^bP = 0.89$) (Table 3).

Postoperative Data

Hemoglobin levels on the first day after surgery in the T_1 group were higher compared to group C (112.4±9.1 vs 104±14.0, $^aP<0.05$). Hemoglobin levels on the first day after surgery in the T_2 group were also higher compared to group C (111.9±9.7 vs 104±14.0, $^aP<0.05$). There was no statistical difference in hemoglobin levels on the first day after surgery in the T_2 group compared to the T_1 group

(^{b}P> 0.05). This suggests that both the two doses of tranexamic acid reduces intraoperative bleeding. There was no significant difference in platelet counts among the three groups of patients on the first day after surgery (P> 0.05). There was a statistically significant difference in prothrombin time on the first day after operation in the T_1 group compared to the control group (15.36±1.48 vs 12.68±1.46, ^{a}P<0.05) and was similar in the TA_2 group (15.29±3.30 vs 12.68±1.46, ^{a}P<0.05). Compared to the T_1 group, there was no significant difference in prothrombin time on the first day after surgery in the T_2 group (15.36±1.48 vs 15.29±3.30, ^{b}P> 0.05). There was no significant difference in activated partial thromboplastin time among the three groups of patients on the first day after surgery (P> 0.05) (Table 4).

Postoperative TEG data were comparable among the three groups. There was no significant difference in the coagulation reaction time (R) among the three groups of patients on the first day after surgery (P> 0.05). In addition, there was no significant difference in clotting time (K) (P>0.05). However, the K value in the control group was relatively high on the first day after surgery (K> 4) and suggested that the fibrinogen function was low. Compared to the control group, the MA value of the T_1 group was statistically significant (55.25±10.41 vs 37.86±13.77, ^{a}P<0.05). The MA value in the control group was lower than 45mm which indicated that platelet function was low. The MA value was not statistically significant between the T_1 and T_2 groups (55.25±10.41 vs 52.02±8.71, ^{b}P> 0.05).

Compared to the control group, the coagulation index (CI) in the T_1 group was statistically significant (0.49±2.16 vs -4.06±2.84, $^aP<0.05$). This indicated hypo-coagulation in the control group on the first day after surgery. There was no significant difference in the coagulation index (CI) between the T_2 group and the control group ($P> 0.05$) and the coagulation index (CI) in the T_2 group was not statistically different compared to the T_1 group ($P> 0.05$) (Table 4).

Drainage Volume and Transfusion Outcomes

Compared to the control group, the difference in drainage volume at 6 hours after surgery in the T_1 group (106.9±34.5 vs 241.4±37.9,$^aP<0.05$) and T_2 group (124.8±64.2 vs 241.4±37.9,$^aP<0.05$) was statistically significant. This suggested that the two doses of tranexamic acid could reduce drainage after 6 hours. There was no statistically significant difference in drainage volume at 6 hours after surgery in the T_2 group compared to the T_1 group (106.9±34.5 vs 124.8±64.2, $^bP> 0.05$). In addition, the drainage on the first postoperative day and the amount of red blood cells transfused were similar between the two treatment groups. There was no significant difference in plasma volume infusion on the first day of operation among the three groups ($P> 0.05$). No platelet transfusions were performed for all three groups (Table 5).

Secondary Outcomes and Adverse Events

Compared to the control group, the postoperative intensive care unit (ICU) stay in the T_1 group

was statistically significant (1.5±0.12 vs 2.65±0.22^{a}P<0.05). In addition, the ICU stay in the T_2 group was shorter compared to the control group(1.5±0.12 vs 2.65±0.22, ^{a}P<0.05). Compared to the T_1 group, there was no significant difference in ICU stay after surgery in the T_2 group (^{b}P> 0.05). Epilepsy, as a major adverse outcome measure, was not observed in all the three groups.

DISCUSSION

In this study, we determined the effects of two different doses of tranexamic acid during cardiac valve replacement under CPB. Compared to the control group, tranexamic acid administered to patients reduced intraoperative and postoperative bleeding and perioperative blood product infusion volume.

Massive blood transfusion in cardiovascular surgery directly affects patient prognosis. The purpose of blood transfusion itself is to increase the oxygen-carrying ability of the blood and improve blood coagulation function. This is an important treatment strategy. However, due to limited blood supplies, preventing the use of blood transfusions is a necessity. Tranexamic acid may play a role in the plasmin pathway, rather than just inhibiting the dissolution of fibrin. However, the exact mechanism has not been fully elucidated.(13, 14) In addition, tranexamic acid has been shown to reduce plasma concentrations of plasmin by blocking the lysine binding site of plasminogen and

hence protecting some platelet function.(15)

During CPB, the activation of coagulation factors induces the release of tissue plasminogen activator from endothelial cells and subsequently induces fibrinolysis. Cardiac surgery performed under CPB may cause serious complications, of which bleeding is the most common complication.(16) Under normal physiological conditions, fibrinolysis occurs when tissue plasminogen activator is released from the endothelium. This in turn induces the conversion of plasminogen to plasmin, which is an active protease that cleaves fibrin.(17)Since the withdrawal of aprotinin from the market, the use of tranexamic acid during cardiac surgery with CPB has increased. The main purpose is to reduce perioperative bleeding. However, the optimal dose that should be administered to patients has not been determined. (17)

The use of tranexamic acid as an antifibrinolytic drug in conventional heart surgery is aimed at inhibiting the solubilizing activity of fibrin, reducing the amount of blood loss in surgical patients and the demand for allogeneic blood products.(18)Hence, antifibrinolytic drugs are routinely used in cardiac surgery to reduce intraoperative and postoperative bleeding. However, there are concerns that TXA may be associated with clinical seizures and may be dose-related even at smaller doses (50 mg per kilogram).(8, 17, 19) However, multiple factors result in seizures after cardiac surgery, even without the use of tranexamic acid(20, 21). In this study, we selected two different doses of

tranexamic acid as hemostatic agents for cardiac surgery under CPB. We did not observe epilepsy in any of the three groups of patients after cardiac valve replacement.

We then compared thromboelastography indexes and the coagulation status of the three groups after surgery. They suggested that patients in the control group on the first day after surgery had low coagulation factor activity, lower platelet function, and diminished fibrinogen function. We used thromboelastography to monitor patients before and after cardiac surgery to further evaluate the patient's coagulation status. Thromboelastography better estimates the patient's coagulation status and can guide clinicians to regulate blood transfusions based on the results. This makes clinical blood transfusions more standardized and avoids the clinical abuse of blood products and reduces the risk of related complications that blood transfusions may bring.

Certain limitations of the current study need to be mentioned. This was a single-center study. Our results should be replicated in multi-center clinical studies to obtain more meaningful data and conclusions. Because of the limitations of clinical trials, this study was not double-blind study, which may lead to biased results. Second, the use of thromboelastography needs to be further demonstrated. Monitoring and evaluations at certain time points during CPB may be a better guide for intraoperative blood transfusion. Third, the follow-up period of this study was short and there was no further follow-up on the patients' quality of life after discharge. This study was based on adult cardiac surgery,

hence, the use of TXA in pediatric cardiac surgery patients remains empirical. In addition, bleeding in pediatric cardiac surgery patients is more common compared to adults(22, 23). A previous study demonstrated the pharmacokinetics of TXA in children undergoing cardiac surgery with CPB(22). However, the optimal dose of TXA which is most effective and safe for children of multiple ages needs to be determined.

CONCLUSIONS

The two different doses of tranexamic acid administered during cardiac valve replacement surgery under CPB in this study were able to reduce intraoperative bleeding as well as the amount of blood transfusion required during surgery. The reduction in bleeding reduced the amount of red blood cell transfusion required after surgery and it reduced the length of ICU stay. There was no significant difference in the effectiveness of the two tranexamic acid doses in reducing bleeding and infusion of red blood cells.

No differences in platelet transfusion and plasma transfusion were observed among the three groups in this study. Assessing the coagulation function through thromboelastography could make it easier to implement perioperative blood protection strategies and thus standardize blood transfusions.

308 **LIST OF ABBREVIATIONS**

TXA	Tranexamic acid
TEG	Thromboelastography
CPB	cardiopulmonary bypass
ICU	intensive care unit
FFP	fresh frozen plasma
CABG	coronary artery bypass graft
ASA	American Society of Anesthesiologists
NYHA	the New York Heart Association
TCI	target controlled infusion
HB	hemoglobin
Hct	hematocrit
PLT	platelet
APTT	activated partial thromboplastin time
PT	prothrombin time
FIB	fibrinogen levels

CI	coagulation index

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the clinical medical research Ethical Committee of The First Affiliated Hospital of Anhui Medical University(PJ-06-12(1)) and was registered at the Chinese Clinical Trial Registry (Registration number: ChiCTR-IOR-17012425). All patients signed informed consent.

Consent for publication

The study was explained to the patients, and informed consent was obtained, either on paper or electronic form.

Availability of data and materials

The datasets generated during and analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing Interests

All authors declare that they have no competing interests.

Funding

This study received no specific funding.

Authors' contributions

XX X carried out the studies, participated in collecting data, and drafted the manuscript. XX X and LJ C performed the statistical analysis and participated in its design. XQ C, SR S and MY L participated in acquisition, analysis and interpretation of data. All authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank the Anesthesia team of the Department of Cardiac Surgery, the First Affiliated Hospital of Anhui Medical University for their assistance during the study.

References:

1. Robich MP, Koch CG, Johnston DR, Schiltz N, Chandran Pillai A, Hussain ST, et al. Trends in blood utilization in United States cardiac surgical patients. Transfusion. 2015;55:805-14.

2. Divatia J. Blood transfusion in anaesthesia and critical care: Less is more! Indian J Anaesth. 2014;58:511-4.

3. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. British journal of haematology. 2004;126:139-52.

4. Casbard AC, Williamson LM, Murphy MF, Rege K, Johnson T. The role of prophylactic fresh

frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. Anaesthesia. 2004;59:550-8.

5. Parr KG, Patel MA, Dekker R, Levin R, Glynn R, Avorn J, et al. Multivariate predictors of blood product use in cardiac surgery. J Cardiothorac Vasc Anesth. 2003;17:176-81.

6. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. The New England journal of medicine. 2008;358:2319-31.

7. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg. 2012;93:148-54.

8. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. The New England journal of medicine. 2016.

9. Greiff G, Stenseth R, Wahba A, Videm V, Lydersen S, Irgens W, et al. Tranexamic acid reduces blood transfusions in elderly patients undergoing combined aortic valve and coronary artery bypass graft surgery: a randomized controlled trial. J Cardiothorac Vasc Anesth. 2012;26:232-8.

10. McHugh SM, Kolarczyk L, Lang RS, Wei LM, Jose M, Subramaniam K. A comparison of high-dose and low-dose tranexamic acid antifibrinolytic protocols for primary coronary artery bypass surgery. Indian J Anaesth. 2016;60:94-101.

11. Spiess BD, Gillies BS, Chandler W, Verrier E. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. J Cardiothorac Vasc Anesth. 1995;9:168-73.

12. Ak K, Isbir CS, Tetik S, Atalan N, Tekeli A, Aljodi M, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg. 2009;24:404-10.

13. Levy JH. Antifibrinolytic therapy: new data and new concepts. Lancet (London, England). 2010;376:3-4.

14. Jimenez JJ, Iribarren JL, Lorente L, Rodriguez JM, Hernandez D, Nassar I, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Critical care (London, England). 2007;11:R117.

15. Van Aelbrouck C, Jorquera-Vasquez S, Beukinga I, Pradier O, Ickx B, Barvais L, et al. Tranexamic acid decreases the magnitude of platelet dysfunction in aspirin-free patients undergoing cardiac surgery with cardiopulmonary bypass: a pilot study. Blood Coagul Fibrinolysis. 2016;27:855-61.

16. Hartmann M, Sucker C, Boehm O, Koch A, Loer S, Zacharowski K. Effects of cardiac surgery on hemostasis. Transfusion medicine reviews. 2006;20:230-41.

17. Sigaut S, Tremey B, Ouattara A, Couturier R, Taberlet C, Grassin-Delyle S, et al. Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology. 2014;120:590-600.

18. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. The Cochrane database of systematic reviews. 2011:Cd001886.

19. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010;110:350-3.

20. Goldstone AB, Bronster DJ, Anyanwu AC, Goldstein MA, Filsoufi F, Adams DH, et al. Predictors and outcomes of seizures after cardiac surgery: a multivariable analysis of 2,578 patients. Ann Thorac Surg. 2011;91:514-8.

21. Manji RA, Grocott HP, Leake J, Ariano RE, Manji JS, Menkis AH, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. Can J Anaesth. 2012;59:6-13.

22. Grassin-Delyle S, Couturier R, Abe E, Alvarez JC, Devillier P, Urien S. A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. Anesthesiology. 2013;118:853-62.

23. Guzzetta NA, Allen NN, Wilson EC, Foster GS, Ehrlich AC, Miller BE. Excessive postoperative

bleeding and outcomes in neonates undergoing cardiopulmonary bypass. Anesth Analg. 2015;120:405-10.

Table 1. Preoperative Patient Characteristics

	T_1Group (n=40)	T_2Group (n=36)	C Group (n=35)
Age (y)	52.25±13	51.25±12.98	54.36±10.52
Males/Females	22/18	19/17	19/16
Height (cm)	165.4±6.7	160.1±17.8	163.9±8.0
Body weight (kg)	61.48±8.4	60.75±7.1	57.18±7.5
Ejection fraction (%)	55.5±6.3	51.96±6.1	52.68±7.1

401 **Table 2. Preoperative Laboratory Test Results**

	T_1 Group	T_2 Group	C Group
Hemoglobin (g/l)	133.4±14.9	128.5±15.15	130.4±15.59
Hematocrit (%)	37.06±6.2	36.68±7.2	37.05±5.2
Platelets ($\times 10^9$ /L)	189.9±43.75	190.9±43.88	194.8±59.89
Prothrombin time (s)	13.26±1.2	13.42±1.3	12.78±1.5
APTT (s)	34.63±6.5	33.4±4.0	34.9±5.3
Fibrinogen (g/l)	3.19±0.8	2.84±0.6	3.33±0.8
Coagulation reaction time	4.0±0.6	4.45±1.2	3.7±0.28
Coagulation time	2.35±0.2	2.1±0.9	1.8±0.3
α-Angle	51.6±4.8	57.2±4.1	51.7±8.0
MA	56.65±1.2	55.6±2.1	56±0.9
LY30	0±0	0±0	0±0
Coagulation index	0.55±1.9	0.6±1.3	-0.25±1.7

APTT=activated partial thromboplastin time; MA=Maximum amplitude; LY30=fibrin dissolution rate 30 minutes after MA determination.

405 **Table 3. Intraoperative Data**

Aortic cross-clamp	T_1Group	T_2Group	C Group
Time (min)	91.53±26.11	93.22±24.39	94.37±21.3
CPB time (min)	113.4±27.43	113.2±28.9	120.6±27.63
Protamine dosage (mg)	309.8±59.77	294.7±65.85	292.6±38.68
Hemoglobin levels at the end of CPB (g/l)	94.63±10.03[a]	92.85±8.90[ab]	81.36±9.36
Blood transfusion volume (ml)	518.2±232.8[a]	550±242.5[ab]	741±190.8

406 [a]*P* means $P<0.05$; [b]*P* means $P>0.05$